

WHAT IS CLAIMED IS:

1. A method of identifying selected members of a synthesized library of materials, comprising:

5 (a) providing at least $n*m*f$ solid phase synthesis units, wherein n is equal to a number of choices of different first components in a first stage of synthesis, m is equal to a number of choices of different second components in a second stage of the synthesis, and f is equal to a number of solid phase synthesis units to comprise identical materials upon completion of the synthesis;

10 (b) segregating the solid phase synthesis units into n separate first stage reaction vessels, wherein each separate first stage reaction vessel comprises at least $m*f$ solid phase synthesis units;

(c) reacting the solid phase synthesis units in each of the separate first stage reaction vessels with a different first component in the first stage of the synthesis;

15 (d) segregating the solid phase synthesis units of (c) into m separate second stage reaction vessels by distributing at least one of the solid phase synthesis units from each of the separate first stage vessels into each separate second stage reaction vessel such that each of the separate second stage reaction vessels comprises at least $n*f$ solid phase synthesis units;

20 (e) reacting the solid phase synthesis units in each of the separate second stage reaction vessels with a different second component in the second stage of the synthesis, thereby synthesizing the library of the materials;

(f) detecting one or more distinguishing physical properties of selected members of the library; and,

25 (g) identifying the selected members based on the one or more detected distinguishing physical properties.

2. The method of claim 1, wherein the method is completely or partially computer implemented.

3. The method of claim 1, wherein each different first and second
30 component independently comprises an organic or an inorganic component.

4. The method of claim 1, wherein the library of the materials comprises a combinatorial chemical library.
5. The method of claim 1, wherein the at least $n*m*f$ solid phase synthesis units are subjected to one or more split/pool synthesis steps prior to (a).
- 5 6. The method of claim 1, wherein the solid phase synthesis units each comprise a single particle independently selected from one or more of: a bead, a crown, a piece of paper, a piece of cotton, or a piece of polymer.
7. The method of claim 1, wherein one or more of the solid phase synthesis units comprise single functionalized particles.
- 10 8. The method of claim 1, wherein one or more of the solid phase synthesis units comprise single non-functionalized particles.
9. The method of claim 1, wherein at least two of the solid phase synthesis units comprise single particles having different functionalities attached thereto.
- 15 10. The method of claim 1, wherein at least one of the separate first stage reaction vessels comprises at least two solid phase synthesis units comprising different functionalities.
11. The method of claim 1, wherein each separate first stage reaction vessel in (b) comprises $m*f$ solid phase synthesis units.
- 20 12. The method of claim 1, wherein (b) comprises providing one or more of the at least $m*f$ solid phase synthesis units in one or more two-dimensional arrays in the separate first stage reaction vessels.
13. The method of claim 1 wherein one or more of the at least $m*f$ solid phase synthesis units in one or more of the separate first stage reaction vessels are
- 25 non-arrayed.
14. The method of claim 1, wherein each of the separate second stage reaction vessels in (d) comprises $n*f$ solid phase synthesis units.

15. The method of claim 1, wherein (d) comprises providing one or more of the at least $n*f$ solid phase synthesis units in one or more two-dimensional arrays in the separate second stage reaction vessels.

5 16. The method of claim 1 wherein one or more of the at least $n*f$ solid phase synthesis units in one or more of the separate second stage reaction vessels are non-arrayed.

17. The method of claim 1, wherein the solid phase synthesis units of (d) are randomly arranged in at least one of the second stage reaction vessels.

10 18. The method of claim 1, wherein the solid phase synthesis units of (d) are non-randomly arranged in at least one of the second stage reaction vessels.

15 19. The method of claim 1, wherein each of the separate second stage reaction vessels designates which different second component reacted with the solid phase synthesis units therein to thereby permit structural identification of selected library members upon detecting the one or more distinguishing physical properties of the selected members in (f).

20. The method of claim 1, wherein the solid phase synthesis units each comprise multiple particles combined together.

21. The method of claim 20, wherein an array or a container comprises the multiple particles combined together.

20 22. The method of claim 20, wherein at least one of the multiple particles comprises a non-functionalized solid support.

23. The method of claim 20, wherein at least one of the multiple particles comprises a solid support having one or more functionalities attached thereto.

25 24. The method of claim 20, wherein at least two of the multiple particles comprise solid supports having one or more identical functionalities attached thereto.

25. The method of claim 20, wherein at least two of the multiple particles comprise solid supports having one or more different functionalities attached thereto.

26. The method of claim 1, wherein (a) comprises:

- 5 (i) segregating the at least $n*m*f$ solid phase synthesis units into p separate third stage reaction vessels, wherein p is equal to a number of choices of different third components in a third stage of the synthesis, and wherein each separate third stage reaction vessel comprises at least $n*m*f/p$ solid phase synthesis units;
- (ii) reacting the solid phase synthesis units in each of the separate third stage
10 reaction vessels with a different third component in the third stage of the synthesis; and,
- (iii) combining and mixing the solid phase synthesis units of (ii) in a single pool, thereby providing the at least $n*m*f$ solid phase synthesis units.

27. The method of claim 26, wherein the at least $n*m*f$ solid phase synthesis units comprise $n*m*f*p$ solid phase synthesis units.

15 28. The method of claim 26, further comprising:

- (iv) separating the at least $n*m*f$ solid phase synthesis units of (iii) into $n*m$ separate containers, wherein the $n*m$ separate containers are segregated into the n separate first stage reaction vessels as the solid phase synthesis units of (b).

29. The method of claim 26, further comprising separating the at least
20 $n*m*f$ solid phase synthesis units of (c) into $n*m$ separate containers, wherein the $n*m$ separate containers are segregated into the m separate second stage reaction vessels as the solid phase synthesis units of (d).

30. The method of claims 28 or 29, wherein each of the $n*m$ separate containers comprises multiple particles combined together.

25 31. The method of claim 1, wherein (f) further comprises cleaving the materials from the solid phase synthesis units prior to detecting the one or more distinguishing physical properties.

32. The method of claim 1, wherein the solid phase synthesis units of (e) each comprise multiple particles combined together, and wherein (f) further

comprises separating selected particles from other particles and cleaving synthesized materials from the selected particles prior to detecting the one or more distinguishing physical properties.

5 **33.** The method of claims 1, 31, or 32 , wherein the one or more distinguishing physical properties comprise different molecular masses.

34. The method of claim 33, wherein the different molecular masses are detected by mass spectrometry.

10 **35.** The method of claim 33, wherein structural identification of the selected members comprises determining a fingerprint of library members in one or more of the separate second stage reaction vessels.

15 **36.** The method of claim 33, wherein structural identification of the selected members comprises subtracting a mass of the different second component reacted in a particular separate second reaction vessel from the different detected masses of the selected members to thereby determine masses of different first components included in each of the selected members.

37. The method of claim 36, wherein the structural identification accounts for mass defects of reaction.

20 **38.** The method of claim 33, wherein structural identification of the selected members comprises correlating the different detected masses of the selected members to a physical or logical matrix comprising masses for each individual library member.

39. The method of claim 38, wherein at least one entry in the matrix comprises a summation of masses of different combinations of first and second components.

25 **40.** The method of claim 38, wherein correlations of the different detected masses to entries in the matrix account for mass defects of reaction.

41. The method of claim 38, wherein the correlation is computer implemented.

42. A combinatorial library synthesis system, comprising:

(a) a plurality of reaction vessels;
(b) a handling system configured to translocate solid phase synthesis units and reagents to and from the plurality of reaction vessels;

5 (c) a detection system to detect one or more distinguishing physical properties of selected members of the combinatorial library; and,

(d) a computer operably connected to the handling and detection systems, the computer comprising system software which directs the handling or detection systems to:

10 (i) segregate the solid phase synthesis units into n separate first stage reaction vessels to provide $m \times f$ solid phase synthesis units in each of the n vessels, wherein n is equal to a number of choices of different first components in a first stage of a library synthesis, m is equal to a number of choices of different second components in a second stage of the library synthesis, and f is equal to a number of solid phase
15 synthesis units which comprise identical materials on completion of the library synthesis;

(ii) deliver one or more of the different first components to each of the n separate first stage reaction vessels, thereby providing for reaction of the different first components with the solid phase synthesis units to provide first stage reacted solid
20 phase members;

(iii) segregate the first stage reacted solid phase members from the n separate first stage reaction vessels into m separate second stage reaction vessels by distributing at least one of the first stage reacted solid phase members from each of the separate first stage reaction vessels into each second stage reaction vessels such that
25 each second stage reaction vessel comprises at least $n \times f$ solid phase synthesis units;

(iv) deliver one or more different second components to the second stage reaction vessels, thereby providing for reaction of the different second components with the first stage reacted solid phase members to provide the combinatorial library; and,

(v) detect one or more distinguishing physical properties of the selected
30 members of the combinatorial library.

43. The combinatorial library synthesis system of claim 42, wherein the handling system comprises a bead handler.

44. The combinatorial library synthesis system of claim 42, wherein prior to (i) the system software directs the handling system to:

(1) segregate the at least $n*m*f$ solid phase synthesis units into p separate third stage reaction vessels, wherein p is equal to a number of choices of different third components in a third stage of the library synthesis, and wherein each separate third stage reaction vessel comprises at least $n*m*f/p$ solid phase synthesis units;

(2) deliver one or more of the different third components to each of the separate third stage reaction vessels, thereby providing for reaction of the different third components with the solid phase synthesis units to provide third stage reacted solid phase members; and,

(3) combine and mix the third stage reacted solid phase members in a single pool, thereby providing the solid phase synthesis units for (i).

45. The combinatorial library synthesis system of claim 44, wherein the at least $n*m*f$ solid phase synthesis units comprise $n*m*f*p$ solid phase synthesis units.

46. The combinatorial library synthesis system of claim 44, wherein the system software further directs the handling system to:

(4) separate the solid phase synthesis units of (3) into $n*m$ separate containers, wherein the $n*m$ separate containers are segregated into the n separate first stage reaction vessels as the solid phase synthesis units of (i).

47. The combinatorial library synthesis system of claim 44, wherein the system software further directs the handling system to separate the solid phase synthesis units of (3) into $n*m$ separate containers, wherein the $n*m$ separate containers are segregated into the m separate second stage reaction vessels as the solid phase synthesis units of (iii).

48. The combinatorial library synthesis system of claims 46 and 47, wherein each of the $n*m$ separate containers comprises multiple particles combined together.

49. The combinatorial library synthesis system of claim 42, wherein the system software directs the handling system in (iv) to effect cleavage of combinatorial library members from the solid phase synthesis units.

50. The combinatorial library synthesis system of claims 42 or 49,
5 wherein the one or more distinguishing physical properties comprise different masses.

51. The combinatorial library synthesis system of claim 50, wherein the detection system comprises a mass spectrometer.

52. The combinatorial library synthesis system of claim 51, wherein the computer further comprises at least one database having a logical matrix
10 corresponding to masses of members of a virtual library that are correlated with the detected masses of the combinatorial library members produced by the system to thereby identify chemical structures of the combinatorial library members.

53. The combinatorial library synthesis system of claim 52, wherein correlations account for mass defects of reaction of the detected masses.

15 54. The combinatorial library synthesis system of claim 52, wherein at least one entry in the logical matrix comprises a summation of masses of different combinations of first and second components.